IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Giorgio Terenghi, Pari-Naz, Mohanna, and David P. Martin

Serial No.: 10/568,649 Art Unit: 1649

Filed: February 16, 2006 Examiner: Wang, Chang Yu

For: *POLYHYDROXYALKANOATE NERVE REGENERATION DEVICES*

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REPLY BRIEF

Sir:

This is a Reply Brief to the Examiner's Answer mailed on August 19, 2008. A Request for Oral Hearing was filed on September 9, 2008 and the Commissioner was authorized to charge $1,030.00, the fee for a Request for Oral Hearing for a large entity to Deposit Account No. 50-3129. It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129

APPENDIX AND ARGUMENT: EVIDENCE OF RECORD

The Examiner has stated that the references in the Appendix were not considered because they were not submitted in the Information Disclosure Statement filed August 30, 2006. Copies of the PCT applications cited in the specification of the application at page 2, lines 20, 25 and 27-28 were not submitted. Of these, **WO 01/54593 by Hadlock, et al. has been cited by the examiner in rejecting the claims and must therefore be considered.** Moreover, the references

which provide the most relevant comparative data, as discussed in detail in the Appeal Brief and reiterated below, **were cited in the application at page 2, lines 21-25, were listed in the Information Disclosure Statement and PTO 1449 forms (sheets 15 and 18), which were initialed by the examiner on February 2, 2007, and copies provided. Accordingly, it is legal error for the disclosures of WO 01/54593, Hazari, et al., vol. 24B, J. Hand Surgery, 291-295 (1999); Ljungberg, et al., vol. 19, Microsurgery, 259-264 (1999), and Hazari, et al., vol. 52, British J. Hand Surgery, pp. 653-657 (1999), not to be considered by the examiner.**

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Withdrawal of the rejection of claims 1 and 3-6 under 35 U.S.C. 112 is appreciated.

It is noted that claim 3, which improperly depends from cancelled claim 2, has not been rejected on this basis. Appellants amendment filed February 25, 2008, was intended to correct the dependency to depend from claim 1, but the examiner refused to enter the amendment. The dependency will be corrected should the case be remanded to the examiner.

The remaining issues on appeal are

(i) whether claims 1 and 3-6 are obvious under 35 U.S.C. § 103(a) in view of International Application No. WO 01/54593 by Hadlock, et al. ("Hadlock") in view of Martin, et al., *Biochem. Eng. J.* 16:97-105 (2003) ("Martin").

(ii) whether claims 1 and 3-6 are obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,548,569 to Williams, et al. ("the '569 patent") in view of U.S. Patent No. 5,584,885 to Seckel ("the '885 patent") and evidentiary references Schlossauer, et al., Neurosurgery, 59:740-748 (2006) ("Schlossauer") and Clavijo-Alvarez, et al., *Plast. Reconstr. Surg.*, 119:1839-51 (2007) ("Clavijo").

(iii) whether claims 1 and 3-6 are obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,610,764 to Martin, et al. ("the '764 patent"), U.S. Patent No. 6,838,493 to Williams, et al. ("the '493 patent", the same as U.S.S.N. 10/082,954, US2002/017,358), U.S. Patent No. 6,867,247 to Williams, et al. ("the '247 patent", the same as U.S.S.N. 10/136,499, US2002/017358), or U.S. Patent No. 7,179,883 to Williams, et al. ("the "883 patent") in view of 'the 885 patent and evidentiary references Schlossauer and Clavijo.

(iv) whether claims 1 and 3-6 are rejectable under the judicially created doctrine of non-statutory double patenting in view claims 1-34 of the '764 patent, claims 1-4 and 6-28 of the '493 patent, claims 1-3 and 5-20 of the '569 patent, claims 1-4 and 6-30 of the '247 patent, claims 31 of the '883 patent", claims 1-18 and 21-25 of U.S. Published Application No. 2004/0234576 ("the '576 application), and claims 1-8 of U.S. Published Application No. 2006/0058470.

(7) ARGUMENTS

Appellants affirm all of the arguments made in the Appeal Brief.

(A) The Claimed Invention

(1) Non-obviousness is supported by Unexpected Results

The non-obviousness of the claimed subject matter has previously been discussed in detail below. However, the major reason that the claims drawn to a nerve conduit comprising poly-4-HB (claims 1, 4, 5, and 6) or solely of poly-4-HB (claim 3) is because, in accordance with the criteria defined by the U.S. Supreme Court in *John Deere* and *KSR*, appellants have surprising results.

There is no way anyone could predict from any of the cited art, or the claims, that if one selected this polymer out of the hundreds of PHAs, including the extremely similar

poly-3-HB, one could significantly and unexpectedly and unpredictably increase the rate of neuronal nerve regeneration. The rate of neuronal regeneration for the structurally similar poly-3-HB (see Hazari, et al., vol. 24B, J. Hand Surgery, 291-295 (1999); Ljungberg, et al., vol. 19, Microsurgery, 259-264 (1999), and Hazari, et al., vol. 52, British J. Hand Surgery, pp. 653-657 (1999)) is only 10% at 7 days; 50% at 14 days; with complete regeneration at 30 days. In contrast, as shown by the data in Example 5, 100% regeneration was achieved in 10 days. This is an increase from a rate of regeneration of 0.14 mm/day to 1 mm/day, almost a log factor faster.

(2) Claim 3 is specific to a nerve regeneration device formed solely of P(4HB) and is therefore patentably distinct from the device of claims 1 and 4-6.

The examples are predictive of success for a polymer comprising P(4HB), which releases degradation products that enhance rate of regeneration. However, the examples clearly and unequivocally demonstrate the unexpectedly faster rate of regeneration achieved with a nerve regeneration device formed solely of P(4HB). Therefore, in the event the Board is not persuaded that there is a sufficient showing of unexpected results to support the claims to a copolymer or blend of P(4HB), the claim specific to P(4HB) should still be determined to be non-obvious over the prior art.

(3) The Prior Art Teaches Away from the Claimed Device

Schmidt, et al., *Annu. Rev. Biomed. Eng.*, 5:293-347 (2003) ("Schmidt") (cited by the Examiner in the office action mailed on 2/21/2007), is a review article on neural tissue engineering published two months before the earliest priority date of the present application. Schmidt at least in the paragraph spanning pages 300 and 301 states "Past research in this area (i.e., nerve guide therapies) has focused either on existing natural or synthetic materials;

however, none of the materials studied to dated have matched or exceeded (emphasis added) the performance of the nerve autograft". The Schmidt review considers polymers made of P(3HB) (See Schmidt, Table 1). The examples show nerve regeneration using the claimed device of 1mm/day – this matches nerve regeneration obtained with nerve autografts. No one could have predicted this outcome.

As noted by the Federal Circuit in Eisai (*Supra*), *KSR* presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions. The Federal Circuit cites its recent decision in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008), for elaborating that this latter concept embraces an "easily traversed, small and finite number of alternatives . . . ." Where the art is unpredictable, this element of "identified, predictable solutions" "may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai, supra,* Slip Op. at 8.

Contrary to the examiner's statement on page 7 of the Examiner's Answer, there is no evidence of record that P(4HB) is more stable to hydrolysis in tissue engineering than PHAs in general and P(3HB) in particular, nor that this would enhance nerve repair.

(B) Rejection of claims 1 and 3-6 Under 35 U.S.C. § 103

(1) Claims 1 and 3-6 are not obvious over International Application No. WO 01/54593 by Hadlock, et al. ("Hadlock) in view of Martin, et al., Biochem. Eng. J. 16:97-105 (2003).

Hadlock discloses a neural regeneration conduit that employs spiral geometry. The conduit includes a porous biocompatible support formed into a roll (Hadlock, page 1, lines 20-27). In "rolled architecture" axial channels are replaced by a single spiraling axial space; this provides certain advantages including increased surface area for adherence of neural regeneration (paragraph spanning pages 4 and 5). The support can contain a naturally occurig biological material such as small intestinal mucosa, or it can be a synthetic polymer which include polyhydroxyalkanoates such as polyhydroxybutyrate, polyesters, polylactic acis, biodegradable polyurethanes etc. (Hadlock, paragraph spanning pages 1 and 2).

The polymers listed on page 2 are structurally and chemically distinct from P4HB polymers. In particular, the listed polymers are brittle, rigid, and not suitable for bending or rolling into a tube, in contrast to the elastic P4HB polymers.

Martin is a review article on poly-4-hydroxybutyrate (P4HB) describing some of the progress in the development of the polymer, its properties, uses and potential applications. Martin does not reference nerve guides. Examples of medical devices which can be prepared from the polymers include rods, bone screws, pins, surgical sutures, stents, tissue engineering devices, drug delivery devices, wound dressings, and patches such as hernial patches and pericardial patches. Martin references the use of fibrous meshes for tissue repair, in particular P4HB patches with pore sizes from 180-240 um were prepared for artery augmentation.

Martin does not disclose a neural regeneration tube. Merely disclosing a tube is not sufficient. A tube may be used in place of intestine – inches in diameter; as a ureter – an inch in diameter, as a vascular graft, a quarter or half an inch in diameter. A nerve regeneration tube is significantly smaller.

The combination of Hadlock and Martin does not recite all of the limitations of claims 1 and 3-14. In combination, Hadlock teaches that the chemical nature of the nerve guide is not critical-the support structure can be a biocompatible polymer (see Hadlock, paragraph bridging pages 1 and 2), with the characteristics listed at least on page 6, lines 11-24. Hadlock provides an exemplary list of polymers such as P(3HB), PGA or PLGA, polycaprolacone, polyurethanes, and poly(organo)phosphazenes. Although Hadlock disclose PHAs e.g. P(3HB) as a polymer that can be used for the solid support, one of ordinary skill in the art is aware that there are over 100 different PHA polymers (see for example, Martin, page 98, left col.; or Steinbuchel, et al., *FEMS Microbiol. Lett.*, 128:219-228 (1995), at page 98, a copy of which submitted with the Information Disclosure Statement considered by the Examiner on 2/2/08). There is no reason why one of ordinary skill in the art would look to Martin, and select P(4HB) as the polymer for a nerve regeneration device with any expectation of the superior nerve regeneration obtained by Appellants using P(4HB). There is no reason why one of ordinary skill in the art would select P(4HB) from the over 100 different PHA's known, and from the "any biocompatible polymer" meeting the specifications in Hadlock (page 6, lines 11-24) based on this disclosure in Martin, and expect superior nerve regeneration. As noted above, the advantages were totally unexpected and apparent only after the studies were conducted.

There is no reason to narrow the possible polymers disclosed as application in Hadlock, to P(4HB) disclosed in Martin with any expectation of success in accomplishing nerve

regeneration that matches nerve regeneration obtained with autograph. The results obtained by Appellants could not have been predicted by one of ordinary skill in the art (See Schmidt, cited above). Martin teaches favorable properties of P4HB for use in a number of other types ONCE one knows that they are desirable but the examiner has cited no art that such properties, instead of those relating to the polymers described by Hadlock, are desirable. Thus, there is no reason why one of ordinary skill in the art would select P4HB (Martin), for use as a nerve regeneration device from the disclosure in Hadlock.

Contrary to the Examiner's allegation, there is no discosure in Martin that P(4HB) is more stable and useful (Examiner's Answer, page 6) than P(3HB) for tissue regeneration. Furthermore, according to the Examiner, the expectation of success is provided by the disclosure in Martin that P(3HB) has been evaluated with some success for use in peripheral nerve repair. The Schmidt review considers studies using P(3HB) (see Schmidt, Table 1) in arriving at the conclusion that none of the materials used for nerve conduits have matched the performance of nerve autografts. As noted above, one of ordinary skill in the art has over 100 polymers of PHAs to choose from as well as the numerous types of polymers disclosed in Hadlock. There is no reason to narrow the polymer down to P(4HB), and more importantly, there is no way anyone skilled in the art could predict that if P(4HB) were selected from the large class of PHAs, that it could enhance the rate of regeneration matching the levels obtained with nerve grafts.

(2) The combination of Hadlock and Martin does not recite all of the limitations of claim 5

Claim 5 specifically requires the porosity (not thickness of the device) of the nerve regeneration device to be greater than 5 microns in diameter. Neither Hadlock nor Martin disclose this feature. The porosity of Martin is in the range of 180-240 μm for artery

augmentation; Hadlock does not disclose any porosity, and therefore the combination cannot lead one skilled in the art to the device of claim 5.

(C) Claims 1 and 3-6 are not obvious over U.S. Patent No. 6,548,569 to Williams, et al. ("the '569 patent") in view of U.S. Patent No. 5,584,885 to Seckel ("the '885 patent") and evidentiary references Schlossauer, et al., Neurosurgery, 59:740-748 (2006) ("Schlossauer") and Clavijo-Alvarez, et al., Plast. Reconstr. Surg., 119:1839-51 (2007) ("Clavijo") and

Claims 1 and 3-6 are not obvious over the combination of U.S. Patent No. 6,610,764 to Martin, et al. ("the '764 patent"), U.S. Patent No. 6,838,493 to Williams, et al. ("the '493 patent"), U.S. Patent No. 6,867,247 to Williams, et al. ("the '247 patent"), or U.S. Patent No. 7,179,883 to Williams, et al. ("the "883 patent") in view of 'the 885 patent and evidentiary references Schlossauer and Clavijo.

(1) The Prior Art does not teach the claimed selection

The specification for the foregoing patents is the same, so only one specification (that of the '569 patent) is discussed with specificity. The '569 patent discloses devices formed of or including PHA compositions with controlled degradation rates (*see* abstract). The '569 patent discloses additives that can be used to alter the **degradation rates** of the PHA formulations, such as inorganic acids, additives that form pores, modification of pendant groups or incorporation into the polymer backbone chemical linkages which are more susceptible to hydrolysis or enzymatic attack (from col. 10, line 6 until col. 12, line 15). The '569 patent discloses that polyhydroxyalkanoate nerve guides can be fabricated according to the prior art methods such as the Seckel. There is no disclosure in the '569 patent of porosity for regrowth of nerves, no disclosure of chemical compositions for formation of sheets that can be rolled to form tubes or which are elastic and flexible enough to serve as nerve conduits. There is no disclosure of

selecting a specific chemical composition to alter the rate of neural regeneration. There is no disclosure that P(4HB) is particularly useful for nerve regeneration as compared to any of the other over 100 hundred PHAs. Seckel, upon which the Examiner depends for a method of making neurotubes, does not make up for this deficiency.

It is clear the only way this disclosure can be interpreted to make obvious the claimed subject matter is by using hindsight. This has been repeatedly refuted as inappropriate, however - the references must make obvious the claimed subject matter, not Appellants' own disclosure.

The Examiner's allegation that the Metabolix patents teach the process of forming pore sizes of 80-180 μm for nerve conduits mischaracterizes the disclosure in the these patents. The '569 patent discloses that the rate of polymer degradation (not nerve regeneration) of the devices may be enhanced by additives which form pores and that the diameter of the pore-forming particles may be between nanometers and 500 μm i.e. the range of the pore size is from greater than 0.001 μm to 500 μm and shows an example of how to create such pores using sodium chloride crystals between 80 and 180 μm. There is no disclosure to select from within this wide pore range to arrive at the narrower pore range of 5-500 microns recited in the claims or any expectation that there would be benefits associated with such a pore size selection with respect to nerve regeneration. What is relevant in the '469 patent is the percentage porosity (see Example 4), not the pore size, with devices that are 80% more porous degrading faster-thus, according to the disclosure in the '569 patent, a device with a pore size range of 0.002-0.9 microns, for example, would be expected to show enhanced degradation so long as it is 80% porous.

The '569 patent is concerned with polymers with an altered rate of degradation. The '569 patent discloses that the degradation rates of the polymers cab be manipulated through

(i) addition of various components to the polymeric composition for example

inclusion of acidic additives or excipients (col. 10, lines 7-26)

inclusion of basic additives or excipients (col. 10, lines 7-26)

inclusion of pore forming additives (col. 10, lines 27-41)

use of hydrophobic coatings (from col. 10, line 55 until col. 11, line 5)

(ii) selection of the chemical composition

selection of monomers to be incorporated into the polymer (col. 4, lines 8-10)

(iii) manipulation of the molecular weight (col. 4, line12)

(iv) processing conditions (col. 12, lines 16-22)

for example, solvent casting, melt processing etc

(v) form of the final product

modification of the PHA pendant groups (col. 11, lines 6-31)

alteration of the PHA backbone i.e. incorporation of susceptible linkages into the PHA backbone (col. 11, line 32 until col. 12, line 15).

The Examiner has provided no reason why one of ordinary skill in the art would, from the list methods discussed above, select (i) addition of various components to the polymer, then (ii) further select additives such as pore forming agents and specifically select (iii) a pore size of 5 - 500 microns from the range of nanometer-500 micron pore size disclosed in 'the 569 patent for use in making a chemical composition to alter the rate of neural regeneration.

This is not obvious from any prior art combination.

Schlossauer and Clavijo do not provide any evidence with respect to the pore sizes of a nerve regeneration device. Table 2 of Schlossauer does not mention a pore size range. The pore size range disclosed in Clavijo under Materials and Methods (Clavijo, page 18, right col. 2nd para.), states "To produce hollow polycaprolactone guides and cultiguides, we used a mandrel

coated technique previously described by our group" (citing to studies published in 2004). After briefly discussing the method, Clavijo states "the guides were made 50% porous by the incorporation of sodium chloride crystals (diameter, 30 to 50 μm)". This disclosure is not about a nerve regeneration device, it is about the CultiGuide disclosed in Clavijo; neither Clavijo nor its cited method is prior art to this application.

(2) Secondary considerations including unexpected results support non-obviousness

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, unexpected results, etc.

Various materials such as silicone rubber, polyglactin mesh, acrylic copolymer tubes and other polyesters have been tested as candidates for nerve channel conduits. These however have been reported to include several significant shortcomings (*see* the present specification at least at page 2, lines 5-10). Several researches have investigated the use of poly-3-hydroxybutyrate (P3HB) in a bid to improve upon these results with positive results. Schmidt is a substantive review of neural tissue engineering. However the rate of nerve regeneration obtained with P3HB as well as numerous polymers in the prior art is inferior when compared to the results obtained with a nerve graft (See Schmidt). By combining the polymer and pore size range selection recited in claim 1, the present claims provide a nerve regeneration device with which unexpected nerve regeneration (1mm/day) Thus, the claims provide a nerve regeneration device which has a superior rate of axonal regeneration. The MPEP (§2144.05) states "Appellants can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing "(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004)". The claimed device also

meets the long felt but unmet need for a nerve regeneration device which obtains axonal regeneration that is comparable to that obtained using a nerve graft (*see* the present specification at least at page 3, lines 3-10). Thus, at least for the reasons discussed above, claims 1 and 3-6 are non obvious over the cited art.

Claim 3 must be further assessed separately from claims 1 and 4-6 due to the restriction of the device material to P(4HB) homopolymer.

As discussed above, claim 3 limits the device to the P(4HB) material, which is the exact material used in the working examples in the application as filed showing significantly enhanced rate of regeneration as compared to the closest prior art material P(3HB).

(D) Claims 1 and 3-6 are not obvious over the claims of U.S. Patent No. 6,610,764 to Martin, et al. ("the '764 patent"), U.S. Patent No. 6,838,493 to Williams, et al. ("the '493 patent"), U.S. Patent No. 6,867,247 to Williams, et al. ("the '247 patent"), or U.S. Patent No. 7,179,883 to Williams, et al. ("the "883 patent")

(1) Double Patenting is Legally Improper when the patents are owned by Legally Separate Entities

Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent. *In re Van Ornum*, 214 U.S.P.Q. 761 (C.C.P.A.1982); *In re Zickendraht*, 138 U.S.P.Q. 22 (C.C.P.A. 1963). As discussed below, this situation can only arise if there is common ownership.

The patent rules make clear the necessity for common ownership; and the MPEP affirms this requirement.

37 C.F.R. § 1.321(c)(3) requires that "a terminal disclaimer filed to obviate a judicially created double patenting rejection in a patent application… must…include a provision that any

patent granted on that application…shall be enforceable only for and during such period that said patent is **commonly owned** with the application or patent which formed the basis for the rejection." (emphasis added).

37 C.F.R. 1.78(c) provides "If an application or a patent under reexamination and at least one other application naming different inventors are owned by the same person and contain conflicting claims, and […] if the claimed inventions were **commonly owned**, or subject to an obligation of assignment to the same person, at the time the later invention was made, the conflicting claims may be rejected under the doctrine of double patenting in view of such commonly owned or assigned applications or patents under reexamination." (emphasis added).

There is only one exception to the requirement for common ownership, **where there is a joint research agreement, which is not applicable here**. In describing the analysis that an Examiner must conduct to determine if an obviousness-type double patenting rejection is proper, the MPEP explains:

Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in **a commonly owned patent, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3)**, when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent.

M.P.E.P 804 (II)(B)(1) (emphasis added).

The M.P.E.P elaborates on the common ownership requirement in section 804.03. In this section, the M.P.E.P notes that "[c]laims in commonly owned applications of different inventive entities may be rejected on the ground of double patenting." The M.P.E.P. continues by referring to only one situation in which non-commonly owned applications or an application and a granted

patent may be rejected under obviousness-type double patenting. This situation is when the claims define inventions resulting from activities undertaken within the scope of a joint research agreement. The M.P.E.P. states "Claims may also be rejected on the grounds of nonstatutory double patenting in certain **non-commonly owned applications that claim inventions resulting from activities undertaken with the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(3).**" (emphasis added).

The M.P.E.P. provides further guidance to Examiners regarding when to make a double patenting rejection. The M.P.E.P. explains that when the facts support both rejections, "both a double patenting rejection **based on common ownership** and a rejection based on 35 U.S.C. 102(e)/ 103 prior art" should be made by the Examiner. M.P.E.P §804.03(II)(C) (emphasis added) However, if there is no common ownership, the M.P.E.P. does not instruct the Examiner to make a double patenting rejection. Rather, the M.P.E.P. notes that only a rejection under 35 U.S.C. 102(e)/ 103 prior art should be made first. "Until appellant has established that a reference is disqualified as prior art under the joint research agreement exclusion of 35 U.S.C. 103(c), the examiner should NOT apply a double patenting rejection based on a joint research agreement." M.P.E.P §804.03(II)(C) (emphasis in original).

Accordingly, it is clear that this rejection is legally improper with respect to U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883, all assigned to Metabolix, and which do not share common ownership with the present application. The application in issue is owned by Tepha, Inc., a completely separate company. It is not enough that a person who is named as an inventor on an application assigns to a first company then moves to a second company and then assigns a second application to a second company. Thus, the only possible rejection in view of U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883

could have been made under 35 U.S.C. §102 and/or §103. The 103 rejection has been made and is addressed above.

(2) The Claims are not obvious over the claims of the Metabolix patents U.S. Patent Nos. 6,610,764; 6,838,493; 6,548,569; 6,867,247; and 7,179,883 owned by Metabolix, Inc.

In an obviousness-type double patenting rejection, the question is not whether claims of one application *encompass* those of another, but rather whether the claims of one application are *obvious* in view of the claims of another application. Generally, the analysis required to show such obviousness is the same the analysis required to show obviousness under 35 U.S.C. § 103 (*In re Braithwaite,* 379 F.2d 594, n.2 (CCPA 1967)). Thus, the question is whether it would have been obvious to modify the methods or compositions claimed in the copending applications to arrive at what is presently claimed.

MPEP § 804(II)(B) states "When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure. The specification can be used as a dictionary to learn the meaning of a term in the patent claim". Thus, the Examiner is precluded from using the specification in the double-patenting analysis, except for interpretation of terms in the claims. The reference to the working Examples (Advisory action para. spanning pages 26 and 27) in the specification is not done to explain the meaning of claim terms. The Examiner uses the specification to provide limitations which are absent from the prior art claims. This is impermissible.

The independent claims of each of the Metabolix patents is listed below:

U.S. Patent No. 6,610,764

1. A biocompatible polyhydroxyalkanoate composition that has a controlled degradation rate of less than one year by hydrolysis in vivo, selected from the group consisting of polyhydroxyalkanoate compositions wherein monomeric units are incorporated as chemical linkages into the polymer backbone which alter the chemical stability of the polymer, wherein linkages are incorporated into the polymer backbone which alter the chemical stability of the polymer, and wherein pendant groups are incorporated into the polymer which alter the chemical stability of the polymer, wherein the polyhydroxyalkanoate has a weight-average molecular weight in the range between 10,000 to 10,000,000 Dalton.

12. A biocompatible polyhydroxyalkanoate composition that has a controlled degradation rate of less than one year by hydrolysis in vivo, selected from the group consisting of polyhydroxyalkanoate compositions, wherein monomeric units are incorporated as chemical linkages into the polymer backbone which alter the chemical stability of the polymer and contain more than two functional groups selected from the group consisting of reactive groups which can cleave the polymer backbone by an intramolecular or intermolecular reaction, acidic or basic groups, and units that modulate the reactivity of the ester linkage selected from the group consisting of 2-hydroxyacids, 2-hydroxyethoxy acetic acid, 2-hydroxypropoxy acetic acid, amino acids, amino alcohols, and diacids, which are positioned within the polymer backbone to increase the rate of degradation, triols, and tetraols, wherein linkages are incorporated into the polymer backbone which alter the chemical stability of the polymer, wherein pendant groups are incorporated into the polymer which alter the chemical stability of the polymer, and wherein the

polyhydroxyalkanoate has a weight-average molecular weight in the range between 10,000 to 10,000,000 Dalton.

31. The composition of claim 1 wherein the polyhydroxyalkanoate contains 4-hydroxybutyrate.

32. The composition of claim 1 wherein the polyhydroxyalkanoate is poly(4-hydroxybutyrate).

33. The composition of claim 12 wherein the polyhydroxyalkanoate contains 4-hydroxybutyrate.

34. The composition of claim 12 wherein the polybydroxyalkanoate is poly(4-hydroxybutyrate).

No where is there any mention of a nerve guide regeneration device nor any similar device or teaching. There is nothing that makes *obvious* a P(4HB) nerve regeneration device. It is not enough to disclose the same polymer.

U.S. Patent No. 6,838,493

1. A device comprising a biodegradable polyhydroxyalkanoate polymer composition that has a controlled degradation rate, under physiological conditions, wherein the average molecular mass loss of the polymer decreases 20% to 50% over a ten week time period in vivo or wherein the percent mass loss is greater than 5% over a six week period in vivo, wherein the degradation rate of the polyhydroxyalkanoate polymer is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the polyhydroxyalkanoate polymer has a weight average molecular weight of between 10,000 and 10,000,000 Daltons, and wherein the device is selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, vein

valves, bone marrow scaffolds, meniscus regeneration devices, ligament and tendon grafts, ocular cell implants, spinal fusion cages, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, wound dressings, and hemostats.

4. The device of claim 1 wherein the polyhydroxyalkanoate comprises a polymer selected from the group of consisting of poly-4-hydroxybutyrate, poly-4-hydroxybutyrate-co-3-hydxoxybutyrate, poly-4-hydroxybutyrate-co-2-hydroxybutyrate, and copolymers and blends thereof.

29. A method for making a device that has a controlled degradation rate under physiological conditions, wherein the average molecular mass of the polymer decreases 20% to 50% over a ten week period in vivo or wherein the percent mass loss is greater than 5% over a six week period in vivo, comprising providing a biocompatible polyhydroxyalkanoate composition, as defined by claim 1; and forming or incorporating the polyhydroxyalkanoate composition into a device selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, ligament and tendon grafts, ocular cell implants, spinal fusion cages, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, heart valves and vascular grafts, wound dressings, and hemostats.

The claims here are drawn to a modified PHA, having an altered rate of degradation, which is useful to make a variety of different medical devices. Nerve guides are listed, as are a large number of hydoxy alkanoates that can be be formed into a polymer. There are hundreds if

not thousands of different polymers that can be made and used to form the various devices. The prior art discloses P(3HB) as a preferred nerve guide material. None of the prior art disclose modifying the rate of degradation, however, nor is that defined by the claims pending in this application. Nothing would make obvious the selection of P(4HB) over any other PHA to make a nerve guide, even less without modifying the rate of degradation. There is certainly nothing leading to the unexpectedly advantageous results that selection of P(4HB) to make a nerve guide regeneration device achieves.

U.S. Patent No. 6,548,569

1. A biodegradable polyhydroxyalkanoate composition comprising a polyhydroxyalkanoate polymer having a controlled degradation rate of less than one year in vivo, under physiological conditions, wherein the degradation rate of the polyhydroxyalkanoate polymer is manipulated through addition of components to the polymeric composition, selection of the chemical composition of the polyhydroxyalkanoate polymer through selection of monomeric units, as chemical linkages, which are incorporated into the polymer, by alteration of the linkages, chemical backbone or pendant groups, molecular weight, processing conditions, or form of the composition, and wherein the polyhydroxyalkanoate polymer has a weight average molecular weight of between 10,000 and 10,000,000 Dalton; and wherein the form of the composition refers to the porousness and surface area of the composition.

3. The composition of claim 1 wherein the polyhydroxyalkanoate polymer is selected from the group of consisting of poly-4-hydroxybutyrate, poly-4-hydroxybutyrate-co-3-hydroxybutyrate, poly-4-hydroxybutyrate-co-2-hydroxybutyrate, and copolymers and blends thereof.

None of these claims even mention a tissue engineered device, much less a nerve guide regeneration device. The claims all relate to modification of the degradation rate of a PHA.

U.S. Patent No. 6,867,247

1. A method of enhancing the healing of a wound, injury, or defect in a site in a patient, comprising administering at the site a device comprising a biocompatible polyhydroxyalkanoate composition wherein the degradation rates of the polyhydroxyalkanoates is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the mass loss of the polyhydroxyalkanoate, as measured by gas chromatography, is greater than 5% over a six week period in vivo, or wherein the average molecular mass of the polyhydroxyalkanoate, as measured by gel permeation chromatography, decreases 20% to 50% over a ten week period in vivo, and wherein the device is selected from the group consisting of sutures, suture fasteners, meniscus repair devices, rivets, tacks, staples, screws, bone plates and bone plating systems, surgical mesh, repair patches, slings, cardiovascular patches, orthopedic pins, adhesion barriers, stents, guided tissue repair/regeneration devices, articular cartilage repair devices, nerve guides, tendon repair devices, atrial septal defect repair devices, pericardial patches, bulking and filling agents, ligament and tendon grafts, ocular cell implants, spinal fusion cages, heart valves, vascular grafts, skin substitutes, dural substitutes, bone graft substitutes, bone dowels, wound dressings, and hemostats.

4. The method of claim 1 wherein to polyhydroxyalkanoate comprises a polymer selected from the group of consisting of poly-4-hydroxybutyrate, poly-4-hydroxybutyrate-co-3-hydroxybutyrate, poly-4-hydroxybutyrate-co-2-hydroxybutyrate, and copolymers and blends thereof.

The claims in this patent are clearly drawn to the modification of the degradation rate of a PHA to enhance healing, where the modified PHA is used to form a medical device. These

claims teach away from selecting one of the hundreds of possible PHAs, by teaching that it is the degradation rate that is important for enhancing healing.

U.S. Patent No. 7,179,883

1. A device comprising a biodegradable polyhydroxyalkanoate polymer composition that has a controlled degradation rate of less than one year, under physiological conditions, wherein the degradation rate of the composition is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, wherein the device is selected from the group consisting of rotator cuff repair devices, temporary wound support devices, bladder patches, pledgets, soft tissue reinforcement devices, vascular patches, devices for artrial wall repair, bone marrow scaffolds, ligament repair devices, rods, washers, screws, pins, struts, plates, and staples used in spinal fusion cages, stents, sewing rings, stiffners used in heart valve supports, cell encapsulation devices, coated devices, defect filling devices, organ patches, organ salvage devices, staple line reinforcement devices, pelvic floor reconstruction devices, devices for closure of ventricular septal defects, drug delivery devices, devices for delivery of biological factors, and devices comprising encapsulated proteins, antibodies, enzymes, peptides, polysaccharides, saccharides, organic drugs, inorganic drugs, nucleic acids, antigens, inhibitors, clot dissolving agents, hormones, nucleic acid, and/or lipids.

2. A method for making a device that has a controlled degradation rate of less than one year under physiological conditions, comprising providing a biocompatible polyhydroxyalkanoate composition, wherein the degradation rate of the composition is manipulated through addition of components to the polymeric composition, selection of the chemical composition, molecular weight, processing conditions, or form of the composition, and forming or incorporating the

polyhydroxyalkanoate composition into a device selected from the group consisting of vein valves, rotator cuff repair devices, temporary wound support devices, bladder patches, pledgets, soft tissue reinforcement devices, vascular patches, devices for artrial wall repair, bone marrow scaffolds, meniscus regeneration devices, ligament repair devices, rods, washers, screws, pins, struts, plates, and staples used in spinal fusion cages, stents, sewing rings, stiffners used in heart valve supports, cell encapsulation devices, coated devices, defect filling devices, organ patches, organ salvage devices, staple line reinforcement devices, pelvic floor reconstruction devices, devices for closure of ventricular septal defects, drug delivery devices, devices for delivery of biological factors, and devices comprising encapsulated proteins, antibodies, enzymes, peptides, polysaccharides, saccharides, organic and inorganic drugs, nucleic acids, antigens, inhibitors, clot dissolving agents, hormones, nucleic acid, and/or lipids.

7. The device of claim 1 wherein the polyhydroxyalkanoate comprises a polymer selected from the group of consisting of poly-4-hydroxybutyrate, poly-4-hydroxybutyrate-co-3-hydroxybutyrate, poly-4-hydroxybutyrate-co-2-hydroxybutyrate, and copolymers and blends thereof.

Nerve guide regeneration devices are not mentioned in these claims, only the use of any of hundreds of PHAs for tissue engineering or repair devices. There is nothing leading one skilled in the art to select a P(4HB) instead of any PHA having a modified degradation rate to produce a nerve guide regeneration device which has a hugely increased rate of nerve repair.

(E) Non Staturory double patenting rejections in view of U.S. Published Application Nos. 2004/0234576 ("the '576 application), and 2006/0058470 ("the '470 application) owned by Tepha, Inc. are Moot. The Claims are no longer pending.

(1) U.S. Published Application No. 2004/0234576 (U.S. Serial No. 10/835,926)

Claims 1 and 3-6 of the present application were provisionally rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view of claims 1-18 and 21-25 of U.S. Published Application No. 2004/0234576. Appellants note that this is a provisional rejection. Claims 1-18 and 21-25 of the '576 application have been cancelled. Therefore, this rejection is moot.

(2) U.S. Published Application No. 2006/0058470 (U.S. Serial No. 11/193,580)

Claims 1 and 3-6 of the present application were provisionally rejected under the judicially created doctrine of nonstatutory double patenting as obvious in view of claims 1-8 of U.S. Published Application No. 2006/0058470. Appellants note that this is a provisional rejection. Claims 1-8 are no longer under Examination in the '470 application. In a response to a Restriction Requirement requiring election between claims 9-16 and claims 1-8, of the '476 application, claims 9-16 were elected for prosecution, without traverse. Therefore, the rejection of claims 1 and 3-6 as obvious in view of claims 1-8 of the '470 application is moot.

CONCLUSION

The claims are not anticipated by or obvious over the prior art due to differences between the claimed elements and the unexpected results obtained by selection of P(4HB) polymer as the material for forming a nerve guide.

The claims are not drawn to obvious variants of the Metabolix patent claims.

The rejections for double patenting over the claims in the Tepha patent applications are moot.

Allowance of claims 1 and 3-6 is respectfully solicited.

Respectfully submitted,

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